

Re: Brain Imaging of Eric L. Jeffries

Medical Report of Kirk A. Frey, M.D., Ph.D.

I, The undersigned, declare the following:

1. I am a Staff Physician and Professor in the Departments of Radiology (Division of Nuclear Medicine) and Neurology and a Research Professor in The Mental Health Research Institute at The University of Michigan, Ann Arbor, Michigan.
2. I am a licensed medical practitioner in the State of Michigan and have achieved Board Certification in the fields of Nuclear Medicine (American Board of Nuclear Medicine, 1989) and Neurology (American Board of Psychiatry and Neurology, 1989).
3. My undergraduate studies were at the Massachusetts Institute of Technology, Cambridge, MA, from 1973 to 1977, leading to the S.B. degree in Electrical Engineering (Bioelectrical Engineering Program). I attended medical school and graduate school from 1977 to 1984 at The University of Michigan as a Medical Scientist Training Program Fellow, resulting in M.D. and Ph.D. (Neurosciences) degrees. I trained as an Internal Medicine intern for 1 year at St. Joseph's Mercy Hospital, Ann Arbor, MI, followed by a three-year residency in Neurology and a Fellowship in Nuclear Medicine at The University of Michigan Hospitals.
4. I am an active member of several professional and scientific societies concerned with brain imaging, neurochemistry, and human neurological disorders, including: The Society of Nuclear Medicine; The American Academy of Neurology; The American Neurological Association; The Society for Neuroscience; The International Society for Cerebral Blood Flow and Metabolism; and The European Society of Nuclear Medicine. I am presently an ex-officio member and past President of the Board of Directors of the Brain Imaging Council of The Society of Nuclear Medicine.
5. I am presently on the editorial board of the Quarterly Journal of nuclear Medicine, and have recently completed editorial board assignments in three other prominent medical scientific journals concerned with clinical diagnostic and research brain imaging (including SPECT perfusion and PET metabolism imaging): The Journal of Cerebral Blood Flow and Metabolism; Annals of Neurology; and The European Journal of Nuclear Medicine. I serve as a consultant on the PET Advisory Committee to the US National Institute on Drug Addiction, Addiction Research Center in Baltimore, MD, and have recently served as a consultant to the Montreal Neurological Institute, Brain Imaging Centre. I regularly review research grant applications in brain imaging for the US National Institutes of Health, for the US Department of Energy, and for the Canada Foundation for Innovation.
6. My laboratory at The University of Michigan has been funded by the US National Institutes of Health and other external agencies for over 16 years for the development and application of brain imaging methods to human neurological disorders. We have included studies with Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) over this interval. I have authored over 117 peer-reviewed original scientific articles, 22 book chapters, and 189 preliminary communications or abstracts from our research activities. A current copy of my Curriculum Vitae is appended (Attachment I).
7. In my regular duties at The University of Michigan Medical Center, I supervise and teach medical students, residents and fellows in the use and interpretation of nuclear medicine procedures, including brain SPECT and PET scanning. I am familiar with the current standards of

care and practice regarding the clinical uses of brain imaging, including SPECT and PET. SPECT and PET brain imaging are established diagnostic procedures in a limited number of clinical settings. In many of these, the imaging procedure is not able to independently establish a diagnosis, but rather, serves to refine an established clinical diagnosis made unequivocally on the basis of other information. There are presently no data upon which to rely in the use or interpretation of clinical PET or SPECT imaging procedures for diagnosis of immune cerebritis, cerebral vasculitis, chronic fatigue syndrome, depression, obsessive compulsive disorder or somatization disorder.

8. My opinion (above) is shared by national panels of experts in Nuclear Medicine and Neurology. A recent publication in The Journal of Nuclear Medicine ("Ethical clinical practice of functional brain imaging", The Journal of Nuclear Medicine, 37:1256-1259, 1996; Attachment II) also indicates a lack of established diagnostic criteria for immune cerebritis effects in brain FDG PET or cerebral perfusion SPECT scans. It further states that:

"...while research SPECT and PET studies in patients with mild traumatic brain injury, substance abuse, infectious disease states (such as HIV-related encephalopathies), neurotoxic exposures, environmental illness and foreign body reaction show promise, there is not, as of this writing, adequate evidence to support the use of SPECT or PET in these instances to establish cause-and-effect relationships."

Regarding the use of SPECT brain perfusion studies in forensic settings, the authors state:

"When there are few controlled experimental studies and no available sensitivity and specificity rates, the forensic application of nonreplicated, unpublished, or anecdotal SPECT or PET observations is inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as 'objective evidence' linking neurophysiologic parameters (such as blood flow or metabolism) to a defendant's judgment, insight or motives associated with the commission of a crime, or as an 'offer of proof' of a traumatically caused or substance-induced illness or injury."

9. I have reviewed the brain scans conducted on Eric L. Jeffries, including: brain perfusion SPECT (06/09/2000 - University of Montreal); FDG PET (07/07/2000 - University of California Irvine); brain perfusion SPECT (12/07/2000 - University of Montreal); brain perfusion SPECT (08/05/2003 - Dr. Pretorius); FDG SPECT (08/05/2003 - D. Pretorius). I find that there is no scientific basis for performing any of these imaging tests to evaluate or diagnose immune cerebritis (encephalomyelitis), vasculitis, or chronic fatigue syndrome. Specifically, there are no scientific reports to establish a reliable specific abnormality or pattern of abnormality in patients with proven diagnoses of these conditions. The presence (or absence) of any findings in these PET and SPECT brain imaging tests, thus, has no bearing on the presence (or absence) of these disorders. Furthermore, the brain PET and SPECT imaging tests are not established scientifically as valid diagnostic tools for presence of depression, obsessive compulsive disorder or somatization disorder. Accordingly, the use of PET or SPECT imaging studies is inappropriate and ineffective for the evaluation of these psychiatric diagnoses.

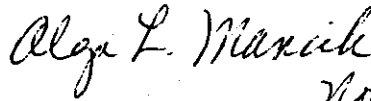
10. There is questionable rationale to technological aspects of the above (see point 9) imaging tests. In the SPECT brain perfusion studies performed at the University of Montreal, the patient was imaged at each of two times (30 min and 2-1/2 hr) after the injection of the ECD radiotracer. ECD uptake by the brain is virtually complete within 15 min after injection and remains essentially unchanged thereafter. The use of 2 scan times per injection is, therefore, not justified nor interpretable. The FDG study performed by Dr. Pretorius presumably employed a modified single-photon nuclear medicine gamma camera, rather than a dedicated PET scanner. The resulting images suggest a severe reduction of the FDG data collected during the scan, and are not of

interpretable quality. The SPECT HMPAO perfusion scan performed also by Dr. Pretorius apparently followed the administration of the cerebral vasodilator drug acetazolamide (Diamox). The rationale for this, and the interpretation of this SPECT scan are unclear. Further, there is no rationale for comparison of the SPECT HMPAO and the FDG in these studies, given the poor technical quality of the FDG images.

11. I offer no clinical diagnostic re-interpretation of the brain imaging tests above (see point 9) at this time, based on my judgment that this is unjustified and medically inappropriate in the evaluation of the clinical entities discussed above. However, I am prepared to do so in the future if specifically requested.



Kirk A. Frey, M.D., Ph.D.



Nov 17, 2003

Professor of Radiology and Neurology
12 November 2003

CURRICULUM VITAE**PERSONAL DATA**

Name: Kirk Andrew Frey, M.D., Ph.D.
Social Security No.: 384-46-0344

EDUCATION

1970-1973 Andover High School, Bloomfield Hills, MI
1973-1977 Massachusetts Institute of Technology, B.S.
(Electrical Engineering)
1977-1984 The University of Michigan School of Medicine, M.D.
1980-1984 The University of Michigan Rackham School of Graduate
Studies, Ph.D. (Neurosciences)

POSTDOCTORAL TRAINING

1984-1985 Intern, Department of Internal Medicine, St. Joseph
Mercy Hospital, Ann Arbor, MI
1985-1988 Resident, Department of Neurology, The University of
Michigan Hospitals, Ann Arbor, MI
1987-1989 Fellow, Division of Nuclear Medicine, Department of
Internal Medicine, The University of Michigan
Hospitals, Ann Arbor, MI
1988-1989 Fellow, Department of Neurology, The University of
Michigan Hospitals, Ann Arbor, MI

ACADEMIC APPOINTMENTS

1986-1989 Research Investigator, Mental Health Research
Institute, The University of Michigan, Ann Arbor, MI
1989-1993 Assistant Professor, Department of Internal Medicine,
Division of Nuclear Medicine, and Department of
Neurology, The University of Michigan Hospitals, Ann
Arbor, MI
1989-1993 Assistant Research Scientist, Mental Health Research
Institute, The University of Michigan, Ann Arbor, MI
1992- Co-Director, Movement Disorders Clinic, Department of
Neurology, The University of Michigan Hospitals, Ann
Arbor, MI
1993-1998 Associate Professor, Department of Internal Medicine,
Division of Nuclear Medicine, and Department of
Neurology, The University of Michigan Hospitals, Ann
Arbor, MI

(Academic Appointments, continued)

1993-1997 Associate Research Scientist, Mental Health Research Institute, The University of Michigan, Ann Arbor, MI

1997-1998 Senior Associate Research Scientist, Mental Health Research Institute, The University of Michigan, Ann Arbor, MI

1998-2000 Professor, Department of Internal Medicine, Division of Nuclear Medicine, and Department of Neurology, The University of Michigan Hospitals, Ann Arbor, MI

1998- Senior Research Scientist, Mental Health Research Institute, The University of Michigan, Ann Arbor, MI

2000- Professor, Department of Radiology, Division of Nuclear Medicine, and Department of Neurology, The University of Michigan Hospitals, Ann Arbor, MI

SENIOR POSTDOCTORAL TRAINING

None

CONSULTING POSITIONS

1995 PET Advisory Committee, NIDA Addiction Research Center, Baltimore

1997 External Advisory Committee, Brain Imaging Center, Montreal Neurological Institute, Montreal, Canada

1997- Scientific Advisory Board, Tourette Syndrome Association

1999 External Advisory Committee, "Clinical Pathophysiology of Acute Brain Injury" NS35966, Washington University School of Medicine, St. Louis, MO

2002- Pfizer Pharmaceuticals, Pain Neuroimaging Research Group Advisory Board

2003 Department of Energy, Biological and Imaging Research, Radiopharmaceutical Research Program

SCIENTIFIC ACTIVITIES

Editorial Boards

1996-2001 *Annals of Neurology*

1996-2002 *Journal of Cerebral Blood Flow and Metabolism*

1999-2002 *Deputy Chief Editor*

1998-2002 *European Journal of Nuclear Medicine*

2003- *The Quarterly Journal of Nuclear Medicine*

Journals Reviewed

Annals of Neurology; Archives of General Psychiatry; Brain; European Journal of Nuclear Medicine; European Journal of Pharmacology; IEEE Transactions on Medical Imaging; Journal of Cerebral Blood Flow and Metabolism; Journal of Neurochemistry; Journal of Neuroscience; Journal of Nuclear Medicine; Lancet; Molecular Pharmacology; Neuroimage; Neurology; Radiology; Stroke

Study Sections and Review Groups

1987 NIH NINCDS, Neurology B, ad hoc reviewer and site visitor
 1988 NIH NCI, ad hoc reviewer
 1992 NIH SBIR, Special Study Section 7: Drug Development and Delivery
 1992 MRC (Canada), Special Review, Montreal Neurologic Institute PET Program
 1993 NIH NCRR, Special Study Section ZRG7 SSS-X (21-22) "3-Dimensional Brain Imaging and Autoradiography"
 1994 NIH NSPA, Special Review Committee, "PET Program Project Grants"
 1994 Review of Clinical Brain Imaging, Intramural NIMH Programs
 1994 NIH NSPB, Special Review Committee, "Human Brain Transplant Therapy for Parkinson's Disease"
 1994 NIH NCRR, Special Study Section ZRG7 SSS-X (36-37) "3-Dimensional Brain Imaging and Autoradiography"
 1995 NIMH Board of Scientific Governors, Review of Intramural Laboratory of Clinical Science, ad hoc member
 1996 NIH NINDS, SRC 06, Special Review Committee, "Clinical Pathophysiology of Acute Brain Injury"
 1996 NIH NCRR, Special Study Section ZRG7 SSS X-72 ☒ Center for Integrative Brain Imaging"
 1997 MRC (Canada), Special Review, Montreal Neurologic Institute Imaging Group Grant
 1997 NIH NCRR GCRC, reviewer and Site visitor, "University of Pittsburgh GCRC"
 1997 NIH NCRR, reviewer and site visitor ZRG7 SSS-9 (8), ☒ Simultaneous PET-MR Brain Imaging and Analysis Research Resource☒
 1997 MRC (Canada), Neurosciences B Study Section
 1997 NIH NINDS, NSPB Special Study Section, "Human Brain Transplant Therapy for Parkinson's Disease"
 1998 NIDCD Board of Scientific Counselors, ad hoc reviewer
 1888 NIH NCRR Reviewer and Site Visitor, ZRG 7 SSS-W (14) "Multidimensional Modeling: A Neuroimaging Resource"
 1998 NIH NCRR GCRC Study Section, ad hoc Member
 1998 MRC (Canada), Neurosciences B Study Section
 1998-2002 NIH NCRR GCRC Study Section
 1998 NIH NINDS, NSPB Special Study Section, "Parkinson's Disease Centers of Excellence"
 1998 MRC (Canada), Neurosciences B Study Section
 1999 MRC (Canada) Special Review Committee: "UBC/Triumf Group Grant"
 1999 NIH NINDS, ZNS1 SRB-K Special Emphasis Panel, "Parkinson's Disease Centers of Excellence"
 1999 NIH NIDA Training and Career Development Committee, ad hoc reviewer
 2000 Canada Foundation for Innovation, Medical Imaging Expert Committee
 2000- Canada Foundation for Innovation, College of Reviewers, Canada Research Chairs
 2002 NIH NIA ZAG1 ZIJ-7 (J3) Special Emphasis Panel, ☒ Aging, Vasculature, Ischemia and Behavior"
 2002 NIH CSR ZRG1 SSS-E (95) Special Emphasis Panel, "Human Brain Project"
 2003 DOE, Radiopharmaceutical and Molecular Nuclear Medicine Science Research - Medical Applications, Review Panel
 2003 Canada Foundation for Innovation, Medical Imaging Expert Committee
 2003 NIH NCRR ZRR1 BT-1 Special Emphasis Panel "Biomedical Research Technology"

GRANT SUPPORT

Past:

DOE, (DE-FG02-87ER60561) (D.E. Kuhl)
"New Techniques for Positron Emission Tomography in the Study of
Human Neurological Disorders"
Principal Investigator: D.E. Kuhl
06/15/87 - 06/14/90
(\$297,132 annual direct costs)
Project 7: "Kinetic Determination of Regional Ligand
Binding"
Project Director: K.A. Frey
(\$49,518 annual direct costs)

NIH, NIMH (P01 MH42652)
"Regulation of Phosphoinositide-Linked CNS Receptors"
Principal Investigator: B.W. Agranoff
04/01/87 - 03/31/92
(\$273,486 annual direct costs)
Project 1: "Regional Regulation of Muscarinic
Receptor Subtypes and Acetylcholine Release"
Project Director: K.A. Frey
(\$63,376 annual direct costs)

NIH, NIMH (P01 MH42652)
"Regulation of Phosphoinositide-Linked CNS Receptors"
Principal Investigator: B.W. Agranoff
07/01/93 - 06/30/96
(\$328,162 annual direct costs)
Project 2: "Muscarinic Receptor Subtype Regulation"
Project Director: K.A. Frey
(\$18,081 annual direct costs)

NIH, NINDS (R01 NS424896)
"Emission Computed Tomography of Local Cerebral Function"
Principal Investigator: D.E. Kuhl; K.A. Frey, Co-Investigator
04/01/89 - 03/31/96
(\$377,802 annual direct costs)

NIH, NINDS (P01 NS 15655)
"PET Study of Biochemistry and Metabolism of the CNS"
Principal Investigator: D.E. Kuhl
12/01/89 - 11/30/94
(\$682,500 annual direct costs)
Project 6: "PET Markers for Muscarinic Cholinergic
Synapses"
Project Director: K.A. Frey
(\$79,072 annual direct costs)

NIH, NIMH (R01 MH47611)
"New PET Radiotracers: Monoamine Reuptake Inhibitors"
Principal Investigator: M.R. Kilbourn; K.A. Frey, Co-Investigator
09/01/91 - 08/31/94
(\$148,394 annual direct costs)

(Grant Support, continued)

NIH, NIMH (R01 MH49748)

"Emission Tomography of Neuropharmacologic Markers"

Principal Investigator: K.A. Frey

08/01/92 - 07/31/94

(\$158,788 annual direct costs)

NIH, NIMH (R01 MH49748)

"Emission Tomography of Neuropharmacologic Markers"

Principal Investigator: K.A. Frey

8/01/96 - 1/31/99

(\$142,346 annual direct costs)

NIH, NIA (P50 AG08671)

"Michigan Alzheimer's Disease Research Center"

Principal Investigator: S. Gilman

6/01/94 - 5/31/99

(\$1,309,660 annual direct costs)

Project 3: "Presynaptic Neurochemical Markers"

Project Director: K.A. Frey

(\$89,988 annual direct costs)

DOE (DE-FG02-87ER60561)

"Advancing PET Science for New Measures of Brain Function"

Principal Investigator: D.E. Kuhl; K.A. Frey, Co-Investigator

01/01/97 - 03/31/00

(\$496,218 annual direct costs)

NIH, NINDS (P50 NS15655)

"PET Study of Biochemistry and Metabolism of the CNS"

Principal Investigator: D.E. Kuhl

07/01/95 - 06/30/00

(\$510,874 annual direct costs)

Project 2: "PET Studies of Parkinson's Disease"

Project Director: K.A. Frey

(\$61,809 annual direct costs)

NIH, NIMH (R01 MH47611)

"New PET Radiotracers: Monoamine Reuptake Inhibitors"

Principal Investigator: M.R. Kilbourn; K.A. Frey, Co-Investigator

05/01/98 - 04/30/01

(\$131,277 annual direct costs)

NIH, NCI (R01 CA59412)

"Robust Anatomic Multimodality Registration"

Principal Investigator: C.R. Meyer; K.A. Frey, Co-Investigator

04/14/97 - 03/31/00

(\$136,140 annual direct costs)

NIH, NINDS (R01 NS34796)

"Earlier vs. Later Elldopa in Parkinson's Disease "

Principal Investigator, U of M Site: K.A. Frey

05/01/97 - 04/30/00

(\$25,373 annual direct costs)

(Grant Support, continued)

DOE (DE-FG02-87ER60561)
"Advancing PET Science for New Measures of Brain Function"
Principal Investigator: D.E. Kuhl; K.A. Frey, Co-Investigator
04/01/97 - 012/31/02
(\$519,443 annual direct costs)

NIH, NCRR (R01 RR13628)
"Enhanced Detection of fMRI Signals via Motion Correction"
Principal Investigator: B. Kim; K.A. Frey, Co-Investigator
07/01/00-06/30/03
(\$200,000 annual direct costs)

Current:

NIH, NIA (P50 AG08671)
"Michigan Alzheimer's Disease Research Center"
Principal Investigator: S. Gilman
9/15/99 - 5/31/04
(\$1,229,665 annual direct costs)
Project 3: "Presynaptic Neurochemical Markers"
Project Director: K.A. Frey
(\$95,732 annual direct costs)

NIH, NCI (R24 CA83099)
"Development of a Regional Tumor Imaging Resource"
Principal Investigator: B. D. Ross; K.A. Frey, Co-Investigator
07/01/99 - 06/30/05
(\$1,092,268 direct costs year 01, \$271,605 years 2 - 5)

NIH, NIDA (R01 DA12458)
"High Doses of Methamphetamine on Human Brain Function"
Principal Investigator: C.R. Schuster (Wayne State University)
01/20/00 - 12/31/03
(\$267,724 annual direct costs)
Principal Investigator, U of M Consortium: K.A. Frey
(\$45,441 annual direct costs)

DOE (DE-FG02-87ER60561)
"Advancing PET Science for New Measures of Brain Function"
Principal Investigator: M.R. Kilbourn; K.A. Frey, Co-PI
01/01/03 - 12/31/03
(\$419,963 annual direct costs) DE-FG02-87ER60561 (M.R. Kilbourn)

NIH, NINDS (P50 NS15655)
"PET Study of Biochemistry and Metabolism of the CNS"
Principal Investigator: K.A. Frey
08/01/01 - 07/31/06
(\$851,216 annual direct costs)

NIH, NCRR (M01 RR00042)
"The University of Michigan General Clinical Research Center"
Principal Investigator: G. Omen; K.A. Frey, Biomedical Imaging
Core Director
12/01/00 - 11/30/05
(\$6,622,796 annual direct costs)

(Grant Support, continued)

NIH, NINDS (R01 NS41061)
"Effect of Spinal Cord Stimulation on Cerebral Blood Flow"
Principal Investigator: O. Sagher; K.A. Frey, Co-Investigator
12/01/00 - 11/30/05
(\$125,000 annual direct costs)

NIH, NINDA (R21 NS43638) (M. Csete)
Erythropoietin Therapy for Parkinson's Disease
02/05/02 - 01/31/04
(\$125,000 annual direct costs)

NIH, NCI (P01 CA85878)
"Brain Tumor Therapeutic Efficacy by Quantitative MR"
Principal Investigator: B.D. Ross; K.A. Frey, Co-Investigator
09/01/01 - 08/31/05
(\$1,666,332 annual direct costs)

Pending:

NIH, NINDS (R01 NS047571-01) (K.A. Frey)
"Tourette Syndrome Association NeuroImaging Consortium"
Principal Investigator: K.A. Frey
12/01/03- 11/30/08
(\$1,570,154 annual direct costs)

CERTIFICATION AND LICENSURE

Medical Licensure: National Board of Medical Examiners (#247271), 1985
State of Michigan (#405130), 1988

Board Certification: American Board of Psychiatry and Neurology, 1989
American Board of Nuclear Medicine, 1989

MILITARY SERVICE

None

HONORS AND AWARDS

1973 National Merit Scholarship Finalist
1977 Tau Beta Pi, Eta Kappa Nu
1981 Chapter Award, Michigan Society for Neuroscience
1980-1984 MSTP Predoctoral Fellowship (University of Michigan)
1984 Sandoz Award for Research in Neurology
1986 Alpha Omega Alpha
1990 Marc Tetalman Memorial Award, Society of Nuclear Medicine
1999- Listed in: *The Best Doctors in America* (Midwest Region): Neurology
and Nuclear Medicine
2000 Early Career Distinguished Achievement Award, The University of
Michigan Medical Center Alumni Society

MEMBERSHIPS AND OFFICES IN PROFESSIONAL SOCIETIES

1981- Society for Neuroscience
1983- American Society for Neurochemistry
1983- International Society for Neurochemistry
1987- American Academy of Neurology
1988- Society of Nuclear Medicine
1996- Brain Imaging Council Board of Directors
2000-2002 SNM House of Delegates (Representative)
1998-2000 Program Committee, Sub-Chair, Clinical Neurology
2000 Brain Imaging Council, Vice-President
2001 Brain Imaging Council, President
1994- American Neurological Association
1998- International Scientific Advisory Committee, Neuroreceptor Mapping

TEACHING ACTIVITIESFellow, House Officer, and Medical Student Instruction

1989- Attending Physician, Nuclear Medicine Clinic (1-2 days/week)
 1989-1991 Attending Physician, Neurology Outpatient Clinics (1/2 day/week)
 1990-1995 Nuclear Medicine Research Conference (1 hr, weekly meeting)
 1990-1993 Clinical PET Brain Imaging Case Conference (2 hr, monthly)
 1991- Attending Physician, Movement Disorders Clinic (1/2 day/week)
 2000- Radiology Resident Lecture Series, Nuclear Medicine Studies (1 hr, monthly meeting)
 2001- Radiology Resident On-Call Proficiency Examination (annual oral examinations)

Graduate Courses

Course Co-Instructor (with Dr. Roger Albin) of Neuroscience/Neurology 731: "Clinical Neurology for Neuroscience Graduate Students" (Medical School and Rackham School of Graduate Studies, 2 credit hours), 1990--2000 (offered every two years)

Course Instructor of Neuroscience 701: "Special Topics - Neuroimaging" (Medical School and Rackham School of Graduate Studies, 2 credit hours), 1998 -- 2000 (offered every two years)

Course Instructor of Neuroscience/Neurology 731: "Clinical Neurology for Neuroscience Graduate Students" (Medical School and Rackham School of Graduate Studies, 2 credit hours), 2002-- (offered every two years)

Other Courses

Course Coordinator and Lecturer: Macy Summer Scholars Program-Neuroscience (1-week course on introductory neuroscience for minority high school students) Lectures: "Introductory Neurobiology", "Neurochemistry", "Neuroimaging", "Parkinson's Disease and Tremor", June 1999

Doctoral Dissertation Committees

James L. Olds (Neurosciences Program, Rackham, 1986), committee member
 Angela K. Thompson (Pharmacology, Rackham, 1991), committee member
 Diana M. Slowiejko (Pharmacology, Rackham, 1995), committee member
 Thierry Vander Borcht (University of Louvain, 1996), co-chair (promoter)
 Jennifer A.F. Kearney (Neurosciences Program, Rackham 1997), committee member
 Elyse S. Kemmerer (Neurosciences Program, Rackham), committee chair

Postdoctoral Trainees

1989-1990 Vjera A. Holthoff, M.D., Max Planck Inst. Neurol., Koln, West Germany
 1989-1990 Alfred Buck, M.D., Dept. Neurology, University Hospital, Zurich, Switzerland
 1989-1990 Stephan F. Taylor, M.D., Dept. Psychiatry, Univ. Mich.
 1989-1991 Kien-S. Lee, M.D., Royal Prince Alfred Hospital, Sydney, Australia
 1989-1993 Jon K. Zubieta, M.D., Dept. Psychiatry, Univ. Mich.
 1991-1992 Donald S. Higgins, M.D., Dept. Neurology, Univ. Mich.
 1992-1995 Page B. Pennell, M.D., Dept. Neurology, Univ. Mich.
 1992-1995 Daniel Murman, M.D., Dept. Neurology, Univ. Mich.

(Postdoctoral Trainees, Continued)

1992-1994 Makiko Ishihara, M.D., Dept. Radiology, Chiba University, Chiba, Japan

1993-1995 Thierry Vander Borcht, M.D., University of Louvain, Brussels, Belgium

1996-1998 Nicolaas Bohnen, M.D., Ph.D., Dept. Internal Med., Div. Nuclear Med., Univ. Mich.

1996-1998 David Rose, M.D., Dept. Nucl. Med., Royal Brisbane Hospital, Brisbane, Queensland, Australia

1998-2001 Masahiko Suzuki, M.D., Ph.D., Jikei School of Medicine, Department of Internal Medicine, Chiba, Japan

2001-2003 Guiyun Wu, M.D., Dept. Radiology, Univ. Mich.

EXTRAMURAL INVITED PRESENTATIONS

- "Quantitative In Vivo Receptor Binding: Theory and Application to the Muscarinic Receptor" in Society for Neuroscience 14th Annual Meeting Symposium, "Receptor Binding Radioautography: Techniques, Limitations, and Recent Data", Anaheim, CA, 1984.
- "The Characterization of the In Vivo Chemistry of Brain Receptor Radiochemicals" in Society of Nuclear Medicine Categorical Seminar, "The Chemistry of Radiopharmaceuticals In Vivo: Methods and State of Characterization", Washington, DC, 1986.
- "Pre- and Postsynaptic Neurotransmitter Studies" in PET and SPECT (Course #218), 40th Annual Meeting, American Academy of Neurology, Cincinnati, OH, April 23, 1988.
- "Cholinergic Receptors" in the First San Raffaele PET Workshop: Neuroreceptors, Inst. Scientifico H. San Raffaele, Milan, Italy, April 24-26, 1989.
- "The Diagnostic Utility of Cerebral and Cardiac PET Studies: Comparison with Other Modalities" in International Symposium on Diagnostic Imaging Modalities, El Instituto Nacional de Pediatría, Mexico City, Mexico, September 28-29, 1989.
- "Pharmacological Interventions in PET Brain Studies" at the 31st Annual Spring Meeting of the Central Chapter of the Society of Nuclear Medicine, Dearborn, MI, April 6-8, 1990.
- "Clinical Positron Emission Tomography (PET) in Disorders of the Central Nervous System" at the 18th Annual Spring Update, Advances in Internal Medicine, The University of Michigan Medical School, Ann Arbor, MI, May 8-11, 1990.
- "Synaptic Neurochemistry: Potential Targets for the Development of New Tracer Imaging Methods" and "Neurochemistry of Alzheimer's Disease and Related Dementias: Results of Metabolic Imaging and Future Application of Ligand Binding Methods" in A Frontiers in Nuclear Medicine Joint Symposium on In Vivo Imaging of Neurotransmitter Functions in Brain, Heart and Tumors, Montreal, Quebec, Canada, August 24-25, 1990.
- "Imaging the Cholinergic System" at the Seventh Annual Course on Brain Chemistry and Behavior: Advances in PET and SPECT Imaging, The Johns Hopkins Medical Institutions, Baltimore, MD, March 14-16, 1991.
- "Pulmonary Scintigraphy in the 1990's: Rational Application of Ventilation/Perfusion Imaging" at the 19th Annual Spring Update, Advances in Internal Medicine, The University of Michigan Medical School, Ann Arbor, MI, April 29-May 3, 1991.
- "PET and SPECT in Epilepsy" and "Nuclear Medicine in Neurology - PET and SPECT in the 90's", Nuclear Medicine in Neurology Workshop, Royal Prince Alfred Hospital, Sydney, Australia, July 19, 1991.
- "Imaging in Patients with Suspected or Proven Dementia" in the Third Annual Meeting of the Institute for Clinical PET, Washington, DC, October 24-26, 1991.
- "Clinical Brain PET Studies", Good Samaritan Hospital, Phoenix, AZ, November 20, 1991.

(Invited Presentations, continued)

"In Vivo Quantification of Neurochemical Markers" in Clinical Neurochemistry (Course #145), American Academy of Neurology, May 3, 1992.

"Benzodiazepine Receptor Imaging in Human Brain", Hammersmith Hospital, London, England, May 15, 1992.

"The Bmax/Kd Ratio" and "Clinical Applications of Benzodiazepine Receptor Imaging" in The Benzodiazepine Receptor in the Brain Studied In Vivo (Symposium), Royal Danish Academy of Sciences & Letters, Copenhagen, Denmark, May 18-19, 1992.

Neurology Session Chairman, Invited Lecturer ("Epilepsy: Applications in Diagnosis and Guidance of Therapy"), and Leader of Physician Workshop in PET Interpretation, Fourth Annual International PET Conference, Institute for Clinical PET, Washington, D.C., October 6, 1992.

Discussion Leader and Panelist, PET Applications in Epilepsy, Positron Emission Tomography Workshop, NINDS, NIH, Bethesda, MD, November 9, 1992.

"Applications of Positron Tomography in the Evaluation of Pharmaceuticals" in: Advances in Delivery of Therapeutic and Diagnostic Agents (Conference), Sydney, Australia, December 9-11, 1992.

"In Vivo Pharmacologic Imaging: New Tracer Methods and Applications", Seminar, Australian Nuclear Science and Technology Organization, Lucas Heights, Australia, December 11, 1992.

"PET Studies of Benzodiazepine Receptors", 6th World Congress of the World Federation of Nuclear Medicine and Biology, Sydney, Australia, October 25, 1994.

"In Vivo Receptor Studies", 6th World Congress of the World Federation of Nuclear Medicine and Biology, Sydney, Australia, October 26, 1994.

"Human Benzodiazepine Binding Site Imaging: Methodology and Applications in Neurologic Disease", Montreal Neurological Institute, Montreal, Quebec, Canada, April 13, 1995

"Mapping of Benzodiazepine Receptors Using PET Imaging", Annual Meeting of the West Virginia Chapter of The Society for Neurosciences, The University of West Virginia, Morgantown, WV, April 20, 1995.

"Neurotransmitter Systems in Brain Disease: Basic Concepts", American Society of Neuroradiology, Chicago, IL, April 25, 1995.

"Functional Neuroimaging in the Diagnostic Evaluation of Dementia", in the 11th Annual Alzheimer's Disease Symposium, The University of Tennessee Graduate School of Medicine, Gatlinburg, TN, June 1, 1995.

"Quantitative Neurochemistry from In Vivo Radiotracer Distributions: Physiologic Considerations and Caveats" in the 9th International Symposium on Radiopharmacology, The University of Michigan Medical Center, Ann Arbor, MI, June 7, 1995.

"PET's Current Role in Brain Imaging vs. SPECT and Functional MRI" in the Seventh Annual Meeting of the Institute for Clinical PET, San Francisco, CA, October 25-29, 1995.

(Invited Presentations, continued)

"Advanced Clinical NeuroPET" (Workshop) in the Seventh Annual Meeting of the Institute for Clinical PET, San Francisco, CA, October 25-29, 1995.

"Co-Registering MRI, CT and PET" (Workshop) in the Seventh Annual Meeting of the Institute for Clinical PET, San Francisco, CA, October 25-29, 1995.

"Sorting out the Dementias" in Advances in Internal Medicine, The University of Michigan Medical School, Ann Arbor, MI, April 29 - May 3, 1996.

"Sorting out the Dementias" Medical Grand Rounds, St. Joseph Mercy Hospital, Pontiac, MI, October 11, 1996.

"Imaging of Vesicular Cholinergic and Monoaminergic Transporters in the Brain" The Eighth International Catecholamine Symposium, Pacific Grove, CA, October 13 - 18, 1996.

"Quantification and Mapping of Benzodiazepine Receptors in Human Brain" in In Vivo Veritas, Understanding Brain Function through the use of Quantitative in vivo Biochemical Techniques, National Institutes of Health, Bethesda, MD, November 16, 1996.

"Parkinson's Disease and the Vesicular Monoamine Transporter Type-2 (VMAT2)" Grand Rounds, Department of Internal Medicine, The University of Michigan, December 5, 1997.

"Movement Disorders: Overview and Review" The 1st Annual Neurology for Psychiatry Residents Day Symposium, Novi, MI, April 5, 1997.

"Parkinson's Disease Update" The 2nd Annual Neurology for Psychiatry Residents Day Symposium, Novi, MI, April 4, 1998.

"PET and SPECT: Methodology: Neuroreceptor Ligands and Models" The 1998 International Symposium on Functional Neuroimaging in the Epilepsies, Atlanta, GA, October 30, 1998.

"Assessment of Clinical Utility and Reimbursement of Functional Neuroimaging Procedures" The 1998 International Symposium on Functional Neuroimaging in the Epilepsies, Atlanta, GA, November 1, 1998.

"The Relationship between Immediate Early Gene Expression and Cerebral Metabolism" American College of Neuropsychopharmacology, Las Croabas, Puerto Rico, December 15, 1998.

"Imaging Benzodiazepines and Benzodiazepine Receptors", NIMH Workshop on Animal Models of Anxiety, Rockville, MD, February 8, 1999.

"Investigation of Dopamine Systems in Human Brain using Positron Emission Tomography", Hammamatsu Medical Center, Hammamatsu, Japan, March 10, 1999.

"Neurochemical Imaging of Alzheimer's Disease", 33rd European Society for Clinical Investigation annual meeting, Milan, Italy, April 10, 1999.

"Imaging of Brain Cholinergic and Monoaminergic Neurons with Vesicular Neurotransmitter Transporter Ligands: Implications for Human Neurodegenerative Disease", in: Function and Pharmacology of the Vesicular Neurotransmitter Transporters (Symposium), Experimental Biology 99, Washington, DC, April 20, 1999.

(Invited Presentations, continued)

Course Organizer and Moderator: "Added Value of Functional Brain Imaging in the Management of Stroke and Dementia", Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 9, 1999.

"Characterization of Cerebrovascular Disease with SPECT and PET: Can Stratification Improve Outcomes and Reduce Complications?" in: Added Value of Functional Brain Imaging in Stroke and Dementia (Continuing Medical Education Course), Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 9, 1999.

"Imaging the Vesicular Monoamine Transporter" in: XIII International Congress on Parkinson's Disease, Vancouver, CA, July 26, 1999.

"Imaging Neurochemistry" in: Biomedical Imaging: Beyond Diagnostics (Symposium), Center for Biomedical Engineering Research, The University of Michigan, Ann Arbor, MI, September 18, 1999.

"Transmitter Imaging in Dementia" in: Third Cologne PET Symposium "Introducing the PET Generation for the Next Century", Max-Planck Institut Fur neurologische Forschung, December 10, 1999, Cologne, Germany.

"Clinical Value of PET and SPECT Imaging in Stroke and Dementia" in: First Symposium on Nuclear Medicine in Neurology, Italian Association of Nuclear Medicine, February 20, 2000, Florence, Italy.

"VMAT2 Imaging in Parkinson's Disease" Department of Neurology Grand Rounds, The University of California at San Francisco, April 12, 2000, San Francisco, CA.

"Update on Diagnosis and Treatment of Parkinson's Disease", Department of Physical Medicine and Rehabilitation, The University of Michigan, November 11, 2000, Ann Arbor, MI

"Neuroimaging of Parkinson's Disease and its Progression", Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, March 13, 2001

"Neuroreceptor Studies in Neurology" in: Mapping Receptors at Work, XX International Symposium on Cerebral Blood Flow, Metabolism and Function/V International Conference on Quantification of Brain Function with PET, Taipei, Taiwan, June 11, 2001

"PET Cases in Neurology/Psychiatry" in: Clinical PET - Read with the Experts, 48th Annual Meeting, Society of Nuclear Medicine, Toronto, Canada, June 25, 2001

"Functional Imaging of Dopamine Transmission: The North American Experience" in: Movement Disorders: From the Problem to the Solution, Categorical Seminar, European Association of Nuclear Medicine Annual Congress, Naples, Italy, August 25, 2001

"Medical Treatment of Parkinson's Disease" in: Parkinson's Disease 2001: An Interdisciplinary Approach. Dept. of Medical Education, The University of Michigan Medical School, East Lansing, Michigan, September 12, 2001.

"PET in Diagnosis and Therapy of Movement Disorders" in: Barcelona PET Conference, Barcelona, Spain, October 5, 2001.

Advances in Neuroimage Analysis: Voxel-Based Approaches, Categorical Seminar in Annual Society of Nuclear Medicine Meeting, Los Angeles, CA, June 15, 2002 (Course Organizer and Seminar Moderator)

"Localization in Ictal SPECT" in: Advances in Neuroimage Analysis: Voxel-Based Approaches, Categorical Seminar in Annual Society of Nuclear Medicine Meeting, Los Angeles, CA, June 15, 2002

"Cholinergic and Dopaminergic Neurotransmission Markers in Dementia" in: Assessment of Brain physiology and pathophysiology by means of Functional Neuroimaging: From Genetic Polymorphism to Endophenotypes, Symposium of the Collegium Internationale Neuro-Psychopharmacologicum, Montreal, Canada, June 24, 2002.

"Functional and Neurochemical Neurochemical Imaging in Movement Disorders" in: Brain Imaging in the 21st Century, Educational Symposium in Annual Society of Nuclear Medicine Mid-Winter Meeting, Hollywood, FL, January 26, 2003.

"PET Imaging of VMAT2: A Biomarker of Nigrostriatal Projection Integrity" in: Quantitative Neurosciences. Models, Algorithms, Diagnostics and Therapeutic Applications, Symposium, University of Florida, Gainesville, FL, February 7, 2003.

"Neurochemical Imaging in Alzheimer's Disease" in: Modern Imaging Technology: Advances in Instrumentation and Molecular Imaging. Satellite Conference of the Society of Nuclear Medicine Annual Meeting, New Orleans, LA, June 20-21, 2003.

"Neurochemical Imaging in Degenerative Dementias": Updates in Functional Imaging in Alzheimer's Disease (Continuing Medical Education Course), Annual Meeting of the Society of Nuclear Medicine, New Orleans, LA, June 22, 2003.

"Imaging Psychostimulant Neurotoxicity" in: The University of Michigan Substance Abuse Research Consortium (UMSARC) Symposium, Ann Arbor, MI, November 4-5, 2003.

"Imaging Progression and Neuroprotection of Parkinson's Disease" in: National Parkinsons Foundation 8th International Symposium on Parkinson Research, New Orleans, LA, November 6-8, 2003.

UNIVERSITY COMMITTEE AND ADMINISTRATIVE SERVICE

1986-1988 Neurology Resident Education Committee
1988- Nuclear Medicine PET Operations Committee
1990- Hospital Cerebral Death Determination Committee
1991-1993 Neurosciences Program Curriculum Committee
1994- Neurology Resident Education Committee
1994-1997 Mental Health Research Institute (MHRI) Executive Committee
1994 MHRI Director Search Committee
1995- Michigan Alzheimer's Disease Research Center, Executive Committee
1995-1998 Biomedical Research Council (BMRC)
1996-1997 BMRC, Associate Chair
1997-1998 BMRC, Chair
1996- Radiology Magnetic Resonance Imaging Research Steering Committee
1997 University Neuroimaging Task Force (OVPR)
1997 Medical School Committee on Joint Graduate Student Recruitment
1997-1998 Cognitive Neuroscience Planning Committee (OVPR)
1998- MHRI Academic Promotions Committee
1998 Presidential Life Sciences Commission
1999- Advisory Council on Clinical Research (ACCR)
2001 ACCR, Interim Chair
1999- General Clinical Research Center (GCRC) Advisory Committee
1999 GCRC Director Search Committee
1999 GCRC Grant Renewal Committee
2000- Department of Radiology Committee on Promotions
2000- Medical School/LS&A Joint Committee on Neuroscience
2001- Department of Radiology Executive Committee
2002 Neurology Chair Research Committee

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Completed Publications in Scientific JournalsPeer Reviewed Scientific Publications

1. Frey KA, Wieland DM, Brown LE, Rogers WL, Agranoff BW: Development of a tomographic myelin scan. *Ann Neurol* 1981; 10:214-221
2. Penney JB, Frey K, Young AB: Quantitative autoradiography of neurotransmitter receptors using tritium-sensitive film. *Eur J Pharmacol* 1981; 72:421-422
3. Penney JB, Pan HS, Young AB, Frey KA, Dauth GW: Quantitative autoradiography of [3H]muscimol binding in rat brain. *Science* 1981; 214:1036-1038
4. Fisher SK, Frey KA, Agranoff BW: Loss of muscarinic receptors and of stimulated phospholipid labeling in ibotenate-treated hippocampus. *J Neurosci* 1981; 1:1407-1413
5. Frey KA, Agranoff BW: Barbiturate-enhanced detection of brain lesions by carbon-14--labeled 2-deoxyglucose autoradiography. *Science* 1983; 219:879-881
6. Pan HS, Frey KA, Young AB, Penney JB Jr: Changes in [3H]muscimol binding in substantia nigra, entopeduncular nucleus, globus pallidus, and thalamus after striatal lesions as demonstrated by quantitative receptor autoradiography. *J Neurosci* 1983; 3:1189-1198
7. Dauth GW, Frey KA, Gilman S: A densitometer for quantitative autoradiography. *J. Neurosci Meth* 1983; 9:243-251
8. Ehrenkaufer RLE, Agranoff BW, Bieszki J, Frey K, Hays S, Jewett D: Tritium labeling of potential lipophilic myelin probes. *J Labelled Comp Radiopharmaceut* 1984; 21:87-95
9. Gilman S, Dauth GW, Frey KA, Aldridge JW, Penney JB: Basal ganglia glucose metabolic and single neural unit activity in experimental hemiplegia. *Int J Neurol* 1984; 18:79-93
10. Frey KA, Ehrenkaufer RLE, Beaucage S, Agranoff BW: Quantitative *in vivo* receptor binding. I. Theory and application to the muscarinic cholinergic receptor. *J. Neurosci* 1985; 5:421-428
11. Dauth GW, Gilman S, Frey KA, Penney JB: Basal ganglia glucose utilization after precentral ablation in the monkey. *Ann Neurol* 1985; 17:431-438
12. Frey KA, Ehrenkaufer RLE, Agranoff BW: Quantitative *in vivo* receptor binding. II. Autoradiographic imaging of muscarinic cholinergic receptors. *J Neurosci* 1985; 5:2407-2414

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13. Olds JL, Frey KA, Ehrenkaufer RL, Agranoff BW: A sequential double-label autoradiographic method that quantifies altered rates of regional glucose metabolism. *Brain Res* 1985; 361:217-224
14. Frey KA, Hichwa RD, Ehrenkaufer RLE, Agranoff BW: Quantitative *in vivo* receptor binding III: Tracer kinetic modeling of muscarinic cholinergic receptor binding. *Proc Natl Acad Sci USA* 1985; 82:6711-6715
15. Gilman S, Dauth GW, Aldridge JW, Frey KA, Penney JB: Changes in basal ganglia metabolic and neural unit activity and motor cortex ablation. *Neurosurgons* 1985; 5:161-168
16. Gilman S, Dauth GW, Frey KA, Penney JB: Experimental hemiplegia in the monkey: Basal ganglia glucose activity during recovery. *Ann Neurol* 1987; 22:370-376
17. Shimoyama I, Dauth GW, Gilman S, Frey KA, Penney JB Jr: Thalamic, brainstem, and cerebellar glucose metabolism in the hemiplegic monkey. *Ann Neurol* 1988; 24:718-726
18. Evans DA, Niparko JK, Altschuler RA, Frey KA, Miller JM: Demonstration of prosthetic activation of central auditory pathways using [¹⁴C]-2-deoxyglucose. *Laryngoscope* 1990; 100:128-137
19. Sisson JC, Wieland DM, Koeppe RA, Normolle DP, Frey KA, Bolgos G, Johnson J, Van Dort ME, Gildersleeve DL: Scintigraphic portrayal of beta receptors in the heart. *J Nucl Med* 1991; 32:1399-1407
20. Frey KA, Ciliax B, Agranoff BW: Quantitative *in vivo* receptor binding IV: Detection of muscarinic receptor down-regulation by equilibrium and by tracer kinetic methods. *Neurochem Res* 1991; 16:1017-1023
21. Koeppe RA, Holthoff VA, Frey KA, Kilbourn MR, Kuhl DE: Compartmental analysis of [¹¹C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *J Cereb Blood Flow Metab* 1991; 11:735-744
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34. Murman DL, Frey KA: Neuroimaging of epilepsy, movement disorders, and degenerative diseases. *Curr Opin Neurol* 1993; 6:919-926
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